EX-1

EXHIBIT 1

PACKAGE INSERT

ESTROSTEP®
(Norethindrone Acetate and Ethinyl Estradiol Tablets, USP)

ESTROSTEP® 21

(Each white triangular tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol; each white square tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol; each white round tablet contains 1 mg norethindrone acetate and 35 mcg ethinyl estradiol.)

ESTROSTEP® Fe

(Each white triangular tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol; each white square tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol; each white round tablet contains 1 mg norethindrone acetate and 35 mcg ethinyl estradiol; each brown tablet contains 75 mg ferrous fumarate.)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

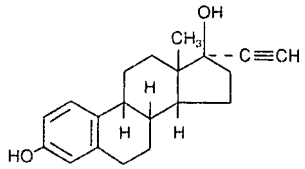
Estrostep is a graduated estrophasic providing estrogen in a graduated sequence over a 21-day period with a constant dose of progestogen.

Estrostep **21** provides for a 21-day dosage regimen of oral contraceptive tablets.

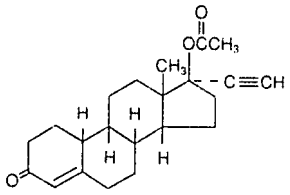
Estrostep **Fe** provides for a continuous dosage regimen consisting of 21 oral contraceptive tablets and seven ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose.

Each white triangle-shaped tablet contains 1 mg norethindrone acetate [(17 alpha)-17 (acetyloxy)-19-norpregna-4-en-20-yn-3-one] and 20 mcg ethinyl estradiol [(17 alpha)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol]; each white square-shaped tablet contains 1 mg norethindrone acetate and 30 mcg ethinyl estradiol; and each white round tablet contains 1 mg norethindrone acetate, 35 mcg ethinyl estradiol. Each tablet also contains calcium stearate; lactose; microcrystalline cellulose; and starch.

The structural formulas are as follows:



Ethinyl Estradiol



Norethindrone Acetate

Each brown tablet contains microcrystalline cellulose; ferrous fumarate; magnesium stearate; povidone; sodium starch glycolate; sucrose with modified dextrins.

Each Estrostep **21** tablet dispenser contains five white triangular tablets, seven white square tablets, and nine white round tablets. These tablets are to be taken [illegible]

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from References 8 and 9 with the authors' permission). For further information, the reader is referred to a text on epidemiological methods.

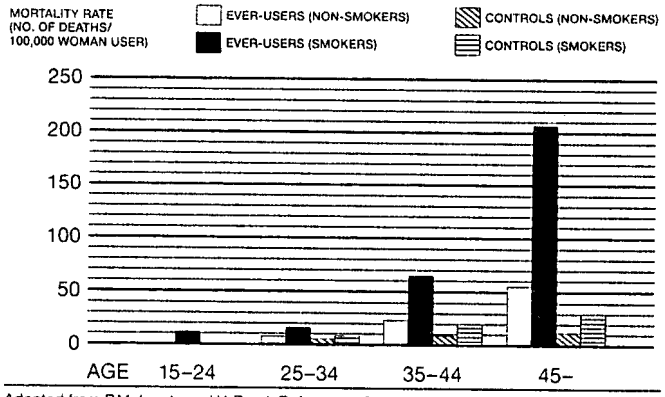
1. Thromboembolic Disorders and Other Vascular Problems

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (10-16). The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases (17). Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 (Table II) among women who use oral contraceptives.

TABLE II
CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN YEARS BY AGE, SMOKING STATUS AND ORAL CONTRACEPTIVE USE



Adapted from P.M. Layde and V. Beral, Reference 18.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity (19). In particular, some progestogens are known to decrease HDL cholesterol, and cause glucose intolerance, while estrogens may create a state of hyperinsulinism (20-24). Oral contraceptives have been shown to increase blood pressure among users (see Section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease (9,10,25-30). Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization (31). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped (8).

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives (15,32). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (15,32). If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in

ESTROSTEP® 21
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ESTROSTEP® Fe
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*Ferrous fumarate tablets are not USP

Studies from Britain have shown an increased (58-60) in long-term (>8 years) oral contracepti ly rare in the U.S., and the attributable risk (the traceptive users approaches less than one per

5. Ocular Lesions

There have been clinical case reports of retinal contraceptives. Oral contraceptives should be complete loss of vision; onset of proptosis or c lesions. Appropriate diagnostic and therapeuti

6. Oral Contraceptive Use Before and

Extensive epidemiological studies have reveale who have used oral contraceptives prior to pre teratogenic effect, particularly insofar as cardia concerned (61,62,64,65), when taken inadverte

The administration of oral contraceptives to in as a test for pregnancy. Oral contraceptives sh threatened or habitual abortion.

It is recommended that for any patient who ha should be ruled out before continuing oral con to the prescribed schedule, the possibility of pr first missed period. Oral contraceptive use sho

7. Gallbladder Disease

Earlier studies have reported an increased ifet of oral contraceptives and estrogens (66,67). M the relative risk of developing gallbladder disea minimal (68-70). The recent findings of minima ceptive formulations containing lower hormoni

8. Carbohydrate and Lipid Metabolic

Oral contraceptives have been shown to cause age of users (23). Oral contraceptives containi hyperinsulinism, while lower doses of estroger gens increase insulin secretion and create insu progestational agents (23,72). However, in the appear to have no effect on fasting blood gluc effects, pre-diabetic and diabetic women shou contraceptives.

A small proportion of women will have persiste discussed earlier (see WARNINGS 1a. and 1d. tein levels have been reported in oral contrace

9. Elevated Blood Pressure

An increase in blood pressure has been report and this increase is more likely in older oral co (74). Data from the Royal College of General P trials have shown that the incidence of hyperte of progestogens.

Women with a history of hypertension or hyper should be encouraged to use another method contraceptives, they should be monitored clos sure occurs, oral contraceptives should be dis pressure will return to normal after stopping or ence in the occurrence of hypertension among

10. Headache

The onset or exacerbation of migraine or deve is recurrent, persistent, or severe requires disc tion of the cause.

11. Bleeding Irregularities

Breakthrough bleeding and spotting are somet contraceptives, especially during the first three